DATA EVALUATION RECORD

GLYPHOSATE

STUDY TYPE: CARCINOGENICITY – MOUSE

OCSPP 870.4200b

ACC. NO. 251007014

Prepared for
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Task Order No. 6-148

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SUPPLEMENTAL DATA EVALUATION RECORD

STUDY TYPE: Carcinogenicity - mice, feeding study
OCSPP 870.4200b [§83-2b]; OECD 451.

PC CODE: 417300 **DP BARCODE:** D430196

TEST MATERIAL (PURITY): Glyphosate (99.7% a.i.)

SYNONYMS: N-(Phosphonomethyl)glycine

CITATION: Knezevich, A.; Hogan, G. (1983) A Chronic Feeding Study of Glyphosate (Roundup Technical) in Mice: Project No. 77-2061: BDN-77- 420. Final rept. (Unpublished study received Aug 17, 1983 under 524-308; prepared by Bio/dynamics, Inc., submitted by Monsanto Co., Washington, DC; CDL:251007-A; 251008; 251009; 251010; 251011; 251012; 251013; 251014). MRID 00130406.

SPONSOR: Monsanto Company, St. Louis, MO 63166

EXECUTIVE SUMMARY:

The original Data Evaluation Record (DER) for this study was prepared in 1983 (TXR No. 004370). This supplemental DER was prepared to include the results of the additional histopathological examinations of the kidney tumors in male mice conducted by a number of independent pathologists and by the Pathology Work Group (TXR No. 005590) and conforms to the current DER format/requirements.

In a carcinogenicity study (MRID 00130406), glyphosate (Technical, 99.7% a.i.) was administered to groups of 50 male and 50 female CD-1 mice/sex/dose in the diet at dose levels of 0, 1000, 5000, or 30,000 ppm (approximately equivalent to 0, 161, 835, 4945 mg/kg bw/day for males and 0, 195, 968, and 6069 mg/kg bw/day for females) for 24 months. Cage-side and detailed clinical observations were done. Body weight and food intake were monitored throughout the study. Water consumption was measured during months 12 and 24. Erythrocyte, as well as total white cell counts and differentials, were done at months 12, 18, and 24. Tissues and organs were collected from all mice whether dying during the study or at terminal sacrifice. Microscopic analyses were done on all collected tissues.

No treatment-related effects were found on survival, body weight, food or water consumption, or hematology parameters of treated male or female mice. The terminal body weight of high-dose males was significantly decreased 9% while the absolute liver weight of high-dose males was

significantly decreased 16%; however, no significant treatment-related effects were found on the liver to body weight ratio. The absolute testes weight of high-dose male mice was increased 7%, while the relative to body testes weight was increased 17%. Neither were statistically significant, and no microscopic histological correlates were found. The incidences of centrilobular hepatocyte hypertrophy were slightly, but not significantly increased in high-dose male mice. Centrilobular hepatocyte necrosis was significantly increased in high-dose males (10/50** (20%) vs control 2/49 (4%), $p \leq 0.01$). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice; however, proximal tubular epithelial basophilia was significantly increased in high-dose females (9/50** (18%) vs control 0/50 (0%), $p \leq 0.01$). No other microscopic treatment-related effects were found.

Based on increased centrilobular hepatocellular necrosis in high-dose males and proximal tubular epithelial basophilia in high-dose females, the systemic LOAEL for male and female CD-1 mice was 30,000 ppm (approximately 4945 mg/kg bw/day for males and 6069 mg/kg bw/day for females). The NOAEL for the study was 5000 ppm (approximately 835 mg/kg bw/day for males and 968 mg/kg bw/day for females).

There was no statistically significant increases in the occurrence of any tumor type in this study. There was a minimal increase in the incidences of the renal tumors in male mice. In 1991, Health Effects Division's Cancer Peer Review Committee (CPRC)s determined that the renal tumors are not treatment-related based on the following weight-of-evidence considerations: The biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls, b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (e.g. tubular necrosis/regeneration, hyperplasia, hypertrophy, etc.), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, and d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females (TXR No. 008897).

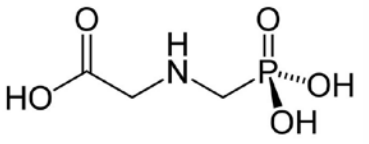
This study was conducted before establishment of the Test Guidelines (OCSPP 870.4200). However, the requirement for carcinogenicity study classified as **Acceptable /Guideline** in combination with another study in CD-1 mice (MRID 49631702).

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were not provided. The study was conducted prior to establishment of US EPA GLP regulations and before US EPA Guideline recommendations contained in OCSPP 870.4200.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: Glyphosate (ROUNDUP® Technical)

Description:	Fine, white clumped powder
Lot/batch #:	Lot Nos. NB 1782608 and NB 1782610
Purity:	99.7% a.i.
Compound stability:	Not reported but was determined by study sponsor
CAS # of TGAI:	1071-83-6
Structure:	

2. Vehicle: Purina Rodent Laboratory Chow #5001

3 Test animals:

Species:	Mice	
Strain:	CD-1, COBS (ICR derived)	
Age/weight at study initiation:	40 days / Males 16 – 28 g, females 15 – 24 g	
Source:	Charles River Breeding Laboratories, Inc., Portage, MI 19081	
Housing:	Individually in stainless steel wire mesh cages during study	
Diet:	Purina Rodent Laboratory Chow #5001, *ad libitum*	
Water:	Elizabethtown Water Co. water, *ad libitum*	
Environmental conditions:	**Temperature:**	18.3 – 23.3°C
	Humidity:	15 - 75%
	Air changes:	Not reported
	Photoperiod:	12 hours light/dark
Acclimation period:	11 days	

B. STUDY DESIGN:

1. In-life dates: Start: March 31, 1980 End: March, 7, 11, or 14, 1982

2. Animal assignment/dose levels: Animals were assigned to the groups shown in Table 1 based on body weight.

Table 1: Study design							
Group	Conc. in diet (ppm)	Approximate average dose Males / Females (mg/kg bw/day) [a]	Range of doses Male / Females (mg/kg bw/day)	Main study (24 months)		Hematology studies at 12, 18, and 24 months	
				Males	Females	Males	Females
Control	0	0 / 0	0 / 0	50	50	10	10
Low	1000	161 / 195	110.9-249.9 / 128.9-287.8	50	50	10	10
Mid	5000	835 / 968	519.3-1264.2 / 689.7-1321.5	50	50	10	10
High	30,000	4945 / 6069	3465.0-7219.8 / 4232.4-9858.6	50	50	10	10

Data from page 34 of Project No. 77-2061

[a] Provided with the "Best Document Available" the approximate average dose was calculated by the reviewer from legible data on pages 100 – 112 of study report. Of a total possible 58 results collected weekly or bi-weekly, N was 57, 55, and 54 for males and 58, 57, and 57 for females in the low-, mid-, and high doses, respectively.

3. **Dose selection:** A dose selection rationale was not located in the study report, but the high dose for both males and females exceeds the limit dose

4. **Diet preparation and analysis:** Diets were prepared weekly by mixing appropriate amounts of test substance with Purina Rodent Laboratory Chow #5001 to generate diets containing 1000, 5000, and 30,000 ppm. Diet storage was not reported. Homogeneity of the test material in the diet was determined from the first diet preparation (March 4, 1980) from triplicate samples collected from the top, middle, and bottom of each preparation by the study sponsor. Diet samples from each preparation were collected weekly for the first month of the study and monthly thereafter for concentration. These were sent to the study sponsor for analyses to determine the stability and concentration of the test material in the preparations (pages 422 – 444 of study report). The performing laboratory also did stability and concentration analyses on all samples (pages 45 – 475 of study report). Both the study sponsor and performing laboratory analyzed diet samples by HPLC collected on Weeks 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, 60, 72, 84, 96, and 102.

Results:

Homogeneity analysis: The coefficient of variation for the 1000, 5000, and 30,000 diets analyzed by the study sponsor from samples collected from the top, middle, and bottom of the mixing chamber ranged from 3.88 – 5.48%, indicating the diets were properly mixed.

Stability analysis: The test material was shown to be stable for the 7-day use of the diets by both the study sponsor and the performing laboratory. Diets analyzed on Day 7 by the study sponsor were 97.2%, 98.8%, and 101.3% of the Day 1 result while diets analyzed by the performing laboratory were 97.9%, 99.0%, and 103.1% of the Day 1 result for the 1000, 5000, and 30,000 ppm diets, respectively, indicating that test material stability was acceptable.

Concentration analysis: Average diet concentration analyses done by the study sponsor were 93.2%, 95.1%, and 96.8% of nominal while those done by the performing laboratory were 92.5% 94.6%, and 96.5% of nominal for the 1000, 5000, and 30,000 ppm diets, respectively, indicating that test material concentration was acceptable..

5. **Statistics:** Body weight and body weight gain, food consumption, feed efficiency, water consumption, hematology parameters, terminal organ and body weights, and organ to body weight and organ to brain weight were analyzed statistically. No reference was made to the calculation of incidence data. For the above parameters, statistical evaluations of equality of

means was made by the appropriate one way analysis of variance technique, followed by a multiple comparison procedure if needed. First, Bartlett's test was done to determine if groups had equal variance. If the variances were equal, parametric procedures were used; if not, nonparametric procedures were used. The parametric procedures were the standard one way ANOVA using the F distribution to assess significance. If significant differences among the means were indicated, Dunnett's test was used to determine which means were significantly different from the control. If a nonparametric procedure for testing equality of means was needed, the Kruskal-Wallis test was used, and if differences were indicated a summed rank test (Dunn) was used to determine which treatments differed from the control.

A statistical significance test for trend was also done. In parametric analyses, standard regression techniques with a test for trend and lack of fit were used. In the nonparametric analyses, Jonckheere's test for monotonic trend was used.

The test for equal variance (Bartlett's) was conducted at the 1%, two-sided risk level prior to analysis of parametric or nonparametric data. All other statistical tests were conducted at the 5% and 1%, two-sided risk levels.

The reviewer considers the methods used for continuous data appropriate.

C. METHODS:

1. Observations:

1a. Cage-side observations: Animals were inspected twice daily for signs of toxicity and mortality.

1b. Detailed clinical examinations: Detailed clinical examinations were done weekly throughout the study to determine signs of local or systemic toxicity, pharmacological effects and for palpable tissue masses.

2. Body weight: The mice were weighed twice before the start of the study, weekly through 14 weeks of treatment, every other week thereafter, and at terminal sacrifice (fasted).

3. Food consumption and compound intake: Food consumption for each mouse was determined once before the start of the study, weekly through the first 14 weeks of treatment, and every other week through the remainder of the study. Food efficiency ((g/interval divided by the current body weight) × 100) and compound intake (mg/kg bwt/day) were calculated as time-weighted averages from the consumption and body weight gain data. Compound consumption was provided as a range in the study report, however, the reviewer calculated an approximate average compound consumption from data provided in the study report.

4. Water consumption: Water consumption was measured from 10 mice/sex/dose at Month 12 over a 3-day period. Because of the high mortality across all dose groups during Month 24, water consumption was measured on 12 mice/sex/dose for a 3-day period, followed by a 2-day period.

5. **Ophthalmoscopic examination:** Ophthalmoscopic examinations were not done. (Ophthalmoscopic examinations are not required by OCSPP 870.4200.)

6. **Hematology and clinical chemistry:** Blood was collected by retrobulbar puncture under light ether anesthesia from 10 mice/sex/dose from fasted animals during Months 12 and 18. At Month 24, blood was collected from 12 male mice/group and from all surviving female mice/group. In the following table the checked (X) hematological parameters were examined. As much as possible, the same mice were used for each blood collection. Clinical chemistry analyses were not done and aren't required by OCSPP 870.4200.

Hematology:

X	Hematocrit (HCT)	X	Leukocyte differential count*
X	Hemoglobin (HGB)		Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)		Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)		Mean corpusc. volume (MCV)
X	Platelet count		Reticulocyte count
	Blood clotting measurements	X	Erythrocyte morphology
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Minimum required for carcinogenicity studies (Control and HDT unless effects were observed) based on Guideline OCSPP 870.4200 and OECD 451

6. **Urinalysis:** Urinalysis was not done or required by OCSPP 870.4200.

7. **Sacrifice and pathology:** All animals that died prior to, and those sacrificed on schedule by exsanguination under ether anesthesia were subjected to gross pathological examinations and the checked (X) tissues were collected for histological examination. Only tissues collected at terminal sacrifice were weighed (XX organs). All collected tissues of mice dying before scheduled sacrifice (if available) and at terminal sacrifice were examined microscopically for neoplastic and non-neoplastic effects. The following tissues were examined microscopically on 10 mice/sex/group: spinal cord sections (cervical and thoraco-lumbar), and sections through the head (nasal cavity, paranasal sinuses, tongue, oral cavity, nasopharynx, and middle ear).

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
X	Tongue	X	Aorta, thoracic*	XX	Brain (multiple sections)*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (retina, optic nerve)*
X	Jejunum*	X	Thymus	X	GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*	X	UROGENITAL		Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Parathyroids*
	Rectum*	X	Urinary bladder*	X	Thyroids*
XX	Liver*+	XX	Testes*+	X	OTHER
X	Gall bladder* (not rat)	XX	Epididymides*+	X	Bone (sternum and/or femur)
	Bile duct* (rat)	X	Prostate*	X	Skeletal muscle
X	Pancreas*		Seminal vesicle*	X	Skin*
X	RESPIRATORY	XX	Ovaries*+	X	All gross lesions and masses*
X	Trachea*	X	Uterus*+	X	Head
X	Lung*++	X	Mammary gland*		
X	Nose*				
X	Pharynx*				
	Larynx*				

* Required for carcinogenicity studies based on Guideline OCSPP 870.4200.
\+ Organ weight required in carcinogenicity studies.
++ Organ weight required if inhalation route

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** While incidences of yellow staining of the anogenital area, scabbing on the ears, alopecia, excessive lacrimation, displacement of the pupils, and ocular opacities were observe in all groups of male and female mice, none were dose-related and all occurred at low incidences.

2. **Mortality:** As shown in Table 2, survival of male and female mice was not affected by treatment with glyphosate. The mortality incidence demonstrated no dose- or test material-related adverse effects. Survival at 18 months was greater than OCSPP 870.4200 Guideline recommendation of 25%.

Table 2. Percent survival of male and female mice treated up to 24 months with glyphosate

Month	Dietary dose (ppm)			
	0	1000	5000	30,000
Males				
12	82	82	86	92
18	76	62	72	78
24	40	32	34	52
Females				
12	94	92	98	90
18	70	68	84	74
24	40	24	54	46

Data extracted from pages 39 and 44 of Project No. 77-2061 (MRID 00130406)

B. BODY WEIGHT:

The body weight of high-dose male mice was decreased significantly at most weighing intervals throughout the study. As shown in Table 3, the body weight of high-dose male mice was decreased 11% by Week 102 relative to control mice, and the overall body weight gain was decreased by 26%. The body weight gain of mid-dose male mice was decreased 13% by study end relative to control mice, but the body weight was not statistically significant. Although sporadic statistically significant differences from control mice were found in body weight of all groups of treated female mice, the effects were not dose- or treatment-related

Table 3: Mean bodyweight (BW, g) and bodyweight gain (BWG, g) of CD-1 mice treated with glyphosate up to 102 weeks

Treatment period	Dose (ppm)				Dose (ppm)			
	0	1000	5000	30,000	0	1000	5000	30,000
	Males				Females			
BW week 0	22.6[50]	22.8[50]	22.5[50]	22.5[50]	20.3[50]	20.5[50]	19.9[50]	19.6[49]
BW week 13	34.8[48]	33.3*[50]	35.1[50]	33.2**[50]	28.9[50]	29.5[49]	29.3[50]	28.8[50]
BW week 24	35.6[47]	34.7[49]	35.3[48]	35.5[50]	31.0[50]	31.3[48]	30.7[50]	30.9[48]
BW week 52	36.4[41]	35.0[41]	36.1[43]	33.8**[47]	32.3[48]	33.1[46]	30.0**[49]	32.1[45]
BW week 76	38.8[40]	37.1[33]	38.5[39]	37.7[39]	32.6[36]	34.2[37]	32.9[42]	32.1[37]
BW week 102	37.7[18]	37.9[14]	35.7[15]	33.6**[24]	35.1[28 a]	37.6[19 a]	NL [a]	33.6[29 a]
BWG week 1	3.2	2.7*	2.5**	2.0**	1.7	2.1	2.5**	2.8**
BWG week 0-13	12.2	10.5	12.6	10.7	8.6	9.0	9.7	9.2
BWG week 13-24	0.8	1.4	0.2	2.3	2.1	1.8	1.4	2.1
BWG week 24-52	0.8	0.3	0.8	-1.7	1.3	1.8	-0.7	1.2
BWG week 52-76	2.4	2.1	2.4	3.9	0.3	1.1	2.9	0.0
BWG week 76-102	-1.1	0.8	-2.8	-4.1	2.5	3.4	NC	1.5
BWG total	15.1	15.1	13.2	11.1	14.8 [a]	17.1 [a]	NC [a]	14.0 [a]
BWG % control	-	100	87	74	-	116	NC	95

Data adapted from Tables 3 and 4, pages 50 – 83, of Project No. 77-2061 (MRID 00130406)
* $p \leq 0.05$; ** $p \leq 0.01$
[a] Determined at Week 100 for female mice
Numbers in superscript are surviving mice at time interval
NL = Not legible
NC = Not calculated

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption:** Although sporadic statistically significant effects were noted in treated male and female mice, none were dose- or treatment-related.

2. **Compound consumption:** The average time weighted compound consumption calculated by reviewer from legible data is in Table 1.

3. **Food efficiency:** No dose- or treatment-related effects were found on food efficiency during Weeks 0 - 14.

4. **Water consumption:** No dose- or treatment-related effects were found.

D. OPHTHALMOSCOPIC EXAMINATION:

Ophthalmoscopic examinations were not done.

E. BLOOD ANALYSES:

Hematology: No biologically or toxicologically relevant effects were noted on total RBC or WBC counts, HGB, HCT, or platelet counts. WBC differential counts were not located in the study report.

F. URINALYSIS:

Urinalysis was not done.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** As shown in Table 4, the terminal body weight of high-dose male mice at sacrifice was significantly decreased 9% relative to concurrent control mice, while that of mid- and high-dose female mice was increased 19% and 15%, respectively. The decreased terminal body weight of high-dose male mice is associated with a 16% statistically significant decrease in the absolute liver weight relative to control in this group, however, the liver to body weight ratio of high-dose male mice was increased 7% (not statistically significant). In addition, the absolute testes weight of high-dose male mice was increased 7%, while the relative to body testes weight was increased 17%. Neither were statistically significant, and no microscopic histological correlates were found. Other sporadic absolute and/or relative to body weight organ weights were found, however, these were not considered toxicologically relevant as a dose-response was not evident.

   The average body weights of mid- and high-dose female mice were increased 19% and 15% relative to concurrent controls at terminal sacrifice. While the absolute kidney weight of mid- and high-dose female mice were slightly increased 5% and 4%, respectively, the kidney to body weight ratio of these mice were increased 12% and 10%, respectively. No microscopic histological correlates were found. Other sporadic absolute and/or relative to body weight organ weights were found, however, these were not considered toxicologically relevant as a dose-response was not evident.

Table 4: Selected mean absolute (g) and relative (%) organ weights of CD-1 mice treated with glyphosate for 102 weeks

Organ	Dose (ppm)				Dose (ppm)			
	0	1000	5000	30,000	0	1000	5000	30,000
	Males				Females			
Kidney – Absolute								
Mean	0.693[20]	0.682[16]	0.666[16]	0.635[26]	0.489[20]	0.495[12]	0.513[27]	0.511[23]
SD	0.144	0.080	0.130	0.098	0.082	0.068	0.088	0.078
Kidney – Relative								
Mean	2.19	2.09	2.21	2.20	1.90	1.77	1.68*	1.71*
SD	0.47	0.22	0.46	0.29	0.27	0.23	0.24	0.23
Liver – Absolute								
Mean	1.753[20]	1.882[16]	1.488[17]	1.475*[26]	1.339[20]	1.521[12]	1.595[27]	1.393[23]
SD	0.483	1.156	0.179	0.319	0.316	0.401	0.443	0.213
Liver – Relative								
Mean	5.60	5.83	4.88	5.08	5.12	5.37	5.19	4.69
SD	1.80	3.79	0.52	0.95	0.85	1.10	1.19	0.83
Testis – Absolute								
Mean	0.157[20]	0.153[16]	0.158[17]	0.168[26]	-	-	-	-
SD	0.056	0.058	0.059	0.046				
Testis – Relative								
Mean	4.97	4.71	5.23	5.84	-	-	-	-
SD	1.80	1.81	2.10	1.58				
Spleen – Absolute								
Mean	0.089[20]	0.144[16]	0.067[17]	0.064[26]	0.099[20]	0.091[12]	0.136[27]	0.100[23]
SD	0.060	0.217	0.020	0.019	0.056	0.043	0.090	0.064
Spleen – Relative								
Mean	2.84	4.43	2.22	2.22	3.81	3.20	4.37	3.29
SD	2.00	6.59	0.63	0.69	2.05	1.44	2.81	1.98
BW – Terminal								
Mean	32[20]	33[16]	31[17]	29**[26]	26[20]	28[12]	31**[27]	30**[23]
SD	2	2	3	3	4	3	4	3

Data from Tables 15 and 16 on pages 127 - 135 of Project No. 77-2061 (MRID 00130406)
Numbers in superscript = N
* $p \leq 0.05$; ** $p \leq 0.01$

2. **Gross pathology:** No remarkable treatment-related effects were noted at necropsy.

3. **Microscopic pathology:**

   a. **Non-neoplastic**: The only treatment-related increases observed were in centrilobular hepatocyte hypertrophy of high-dose male mice as: 9/49 (18%), 5/50 (10%), 6/50 (6%), and 17/50 (34%) in the control, low-, mid-, and high-dose groups, respectively (no statistical significance). Centrilobular hepatocyte necrosis was significantly increased in high-dose male mice (2/49 (4%), 2/50 (4%), 2/50 (4%), and 10/50** (20%) in the control through high-dose groups, respectively, $p \leq 0.01$). The only non-neoplastic alteration in the urinary tract that occurred with an increased frequency was light-to-mild epithelial hyperplasia of the urinary bladder in males. The incidence was 6%, 6%, 20% and 16% in controls through high-dose, respectively. This was considered unrelated to treatment with glyphosate.

No dose-related increases of centrilobular hepatocyte hypertrophy or necrosis were found in treated female mice. However, proximal tubular epithelial basophilia was significantly increased in high-dose female mice in comparison to controls.

All other tissue alterations occurred sporadically or were considered spurious in distribution. Most were found with approximately equal frequency and severity in contro1 and treated animals, and were judged to be unrelated to glyphosate treatment.

b. Neoplastic: Neoplastic outcomes were of the type commonly encountered in mice of this age and strain. With the possible exception of kidney tumors (renal tubular adenomas) in males, all tumor types were considered spurious and unrelated to treatment.

Table 5. Incidence of Neoplasia in Male Mice Treated with Glyphosate for 24 months

Organ / Effect	Dose (ppm)			
	0	1000	5000	30,000
	Males			
Kidney Renal tubular adenoma	0/49	0/49	1/50	3/50

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

The study author(s) concluded that oral administration of glyphosate to mice at up to 30,000 ppm for 24 months resulted in slightly reduced body weight gain in high-dose males and females. No changes in food consumption, clinical or gross necropsy observations and clinical chemistry parameters were noted, and no neoplasms considered to be related to glyphosate administration were observed.

B. REVIEWER COMMENTS:

In this study, no significant treatment-related effects were found on survival, body weight, food or water consumption, or hematology parameters of treated male or female mice. The incidence of centrilobular hepatocyte hypertrophy was slightly, but not significantly increased in high-dose male mice at terminal sacrifice or if all mice were included in the analyses. Centrilobular hepatocyte necrosis was significantly ($p \leq 0.01$) increased in high-dose male mice (10/50; 20%) compared to controls (2/49; 4%). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice. There was a dose-dependent increase in the proximal tubular epithelial basophilia in female mice; the incidences were: 0/50 (0%) in the controls, 2/50 (4%) at the low dose, 4/50 (8%) at the mid dose, and 9/50 (18%) at the high dose ($p \leq 0.01$). All other tissue alterations occurred sporadically and were found with approximately equal frequency and severity in contro1 and treated animals. These were considered unrelated to glyphosate treatment.

As shown in Table 5, the incidences of renal tubule adenomas were as follows: 0/49 in the controls; 0/49 at the low-dose; 1/50 at the mid-dose and 5/50 at the high dose (TXR No. 004370).

In 1985, the Registrant directed a re-evaluation of the original renal section by a consulting pathologist (Dr. Marvin Kuschner). This evaluation identified a small renal tubule adenoma in one control male (animal number 1028) mouse which was not diagnosed as such in the original pathology report (TXR No. 004855).

In 1986, at the request of the agency, additional renal sections (3 sections/ kidney/ mouse spaced at 150 micron intervals) were evaluated in all control and all glyphosate treated male mice in order to determine if additional tumors were present. The additional pathological and statistical evaluations concluded that the renal tumors in male mice was not compound-related (TXR No. 00590).

Furthermore, the agency requested a review of the kidney lesions by the Pathology Work Group (PWG). The PWG examined the all sections of the kidneys including the additional renal sections. The renal tubular-cell lesions diagnosed by the PWG are presented below in Table 6.

Table 6. Glyphosate: Kidney Tumor- PWG Evaluation

Dose/Tumor Type	Control	1000 ppm	5000 ppm	30,000 ppm
	0 mg/kg/day	157 mg/kg/day	814 mg/kg/day	4841 mg/kg/day
Tubular-cell adenoma	1/49	0/50	0/50	1/50
Tubular-cell carcinoma	0	0/50	1/50	2/50
Combined incidence	1/49 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)

The PWG unanimously concluded that these lesions are not compound-related based on the following considerations: 1) renal tubular-cell tumors are spontaneous lesions for which there is a paucity of historical control data for this mouse stock; 2) there was no statistical significance in a pairwise comparisons of treated groups with the controls and there was no evidence of a significant linear trend, see Table 7; 3) multiple renal tumors were not found in any animal; and 4) compound related nephrotoxic lesions, including preneoplastic changes, were not present in this study (TXR No. 005590).

Table 7. Kidney Tumors in Male CD-1 Mice – PWG Fisher's Exact Test

Dose/Tumor Type	Control	1000 ppm	5000 ppm	30,000 ppm
Adenomas	1/49[a]	0/49	0/50	1/450
(%)	(2)	(0)	(0)	(2)
P =	0.4422	1.00000	1.00000	0.75758
Carcinomas	0/49	0/49	1/50	2/50
(%)	(0)	(0)	(2)	(4)
p =	0.06345	1.00000	0.50505	0.25253
Combined	1/49	0/49	1/50	3/50
(%)	(2)	(0)	(2)	(6)
p =	0.06483	1.00000	0.75758	0.31631

Historical control data from the testing laboratory (Bio-dynamics) during the glyphosate study period (1976-1982) are presented in Table 8.

Table 8. Historical Control Data- Kidney tumors in CD-1 Mice – Bio-dynamics Inc.

Study I.D	A		B		C		D		E		F		G	
Study Period	6/78 - 7/80		12/77-4/80		12/77-3/80		10/78-4/81		11/78-4/81		11/77-4/80		10/77-4/80	
No. Examined	57	54	61	51	53	59	60	60	60	60	60	60	60	60
Tubular Adenoma	0	1	0	0	0	0	0	0	0	2	0	0	0	0

Historical control data from 14 studies conducted between 1977 and 1981 at the testing laboratory indicated that the mouse renal tumors ranged from 0 to 3.3% and the incidence in the current study (3/50; 6%) exceeded the upper limit of the historical control range (TXR No. 007252).

In 1986, the agency requested the FIFRA Scientific Advisory Panel (SAP) evaluate the carcinogenic potential of glyphosate. The panel determined that the data on renal tumors in male mice was equivocal since only small numbers of tumors were found in any group including the high dose, they were only adenomas, and the age-adjusted statistical analysis did not show a carcinogenic effect of glyphosate (SAP Report, 02/24/1986).

In 1991, Health Effects Division's Cancer Peer Review Committee (CPRC) determined that the renal tumors are not treatment-related based on the following weight-of-evidence considerations**:** The biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls, b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (e.g. tubular necrosis/regeneration, hyperplasia, hypertrophy, etc.), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, and d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females (TXR No. 008897).

Based on increased centrilobular hepatocellular necrosis in high-dose males and proximal tubular epithelial basophilia in high-dose females, the systemic LOAEL for male and female CD-1 mice was 30,000 ppm (approximately 4945 mg/kg bw/day for males and 6069 mg/kg bw/day for females). The NOAEL for the study was 5000 ppm (approximately 835 mg/kg bw/day for males and 968 mg/kg bw/day for females).

C. <u>STUDY DEFICIENCIES</u>: None. This study was conducted prior to the establishment of the Test Guidelines.